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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/171,081	12/14/1998	SASA KRANJC	22681-0002	7627
25213	7590	08/09/2004	EXAMINER	
HELLER EHRMAN WHITE & MCAULIFFE LLP 275 MIDDLEFIELD ROAD MENLO PARK, CA 94025-3506			PRATS, FRANCISCO CHANDLER	
			ART UNIT	PAPER NUMBER
			1651	

DATE MAILED: 08/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/171,081

Applicant(s)

KRANJC ET AL.

Examiner

Francisco C Prats

Art Unit

1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 May 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 36,38,41-55 and 95 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 36, 38, 41-55 and 95 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

Art Unit: 1651

DETAILED ACTION

The amendment filed May 19, 2004, has been received and entered. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claims 36, 38, 41-55 and 95 are pending and are examined on the merits.

Claim Rejections - 35 USC § 112

Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "low" in claim 38 is a relative term which renders that claim indefinite. The term "low" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Because the metes and bounds of the claimed subject matter are not clear, a holding of indefiniteness is required.

Art Unit: 1651

Claim Rejections - 35 USC § 102

Claims 36, 38, 42-45, 47, 49, 51 and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Cole et al (U.S. Pat. 4,110,165) taken in light of Stanbury et al (*Principles of Fermentation Technology*, Pergamon Press, New York, 1984, pages 11-25).

Cole discloses processes of making clavulanic acid wherein the claimed microorganism, *Streptomyces clavuligerus*, is cultivated in a fermentation medium. Note specifically the potassium dihydrogen phosphate concentration of 0.1% in the fermentation disclosed in Example 13 at column 23. Note further that about 55% of the dipotassium hydrogen phosphate in the fermentation medium in Example 9, at column 21, is "assimilable" phosphorus, i.e. phosphate, and that therefore the medium in Example 9 contains about 1.10 grams of assimilable phosphorus per liter of medium which is about 0.11% assimilable phosphorus, well within the claimed range concentration. Therefore, in at least Examples 9 and 13, the starting phosphorus concentration is below the claimed amount. Moreover, no phosphorus is added during the fermentation, and the fermentations last for 3-5 days. Thus, the processes disclosed in Examples 9 and 13 necessarily meet the limitation requiring the microorganism to be grown within the claimed phosphorus concentration range, and

Art Unit: 1651

also meet the limitation requiring a decrease in the phosphorus concentration. Moreover Example 9 uses "Arkasoy," or soy flour as the nitrogen source. See column 20, lines 1 and 2.

It is noted that the claims as amended now require the fermentation to comprise a growth phase and a stationary phase. These phases are inherent in any batch fermentation process, including the batch fermentation processes disclosed by Cole. See, e.g. Stanbury at page 11, Fig. 2.1. Moreover, because the claims as amended encompass batch processes wherein phosphorus concentration is simply allowed to decrease with time, as occurs in Cole, Cole's process is considered to anticipate the newly added requirement regarding the phosphorus concentration during the growth phase. A holding of anticipation over the cited claims is therefore required.

All of applicant's argument regarding this ground of rejection has been fully considered but is not persuasive of error. While applicant asserts that the phosphorus concentrations in Cole's examples are not necessarily present at the beginning of the fermentations, applicant does not provide evidentiary support for this assertion. Moreover, given the disclosure of the reference, it seems fairly clear that the claimed phosphorus concentrations are in fact present at the start of the Cole's fermentations. As to whether the process

Art Unit: 1651

disclosed by Cole "maintains" the phosphorus concentrations within specific parameters, note again that in the described embodiments, Cole starts within the claimed phosphorus concentration range and does not add phosphorus, thereby allowing the concentration to decrease. This clearly reads on applicant's invention as recited in the rejected claims.

Claim Rejections - 35 USC § 103

Claims 36, 38, 41-47, 49-54 and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cole et al (U.S. Pat. 4,110,165).

As discussed above, Cole is considered to anticipate claims 36, 38, 42-45, 47, 49, 51 and 52, because Cole discloses processes of making clavulanic acid wherein the claimed microorganism, *Streptomyces clavuligerus*, is cultivated in a fermentation medium containing the claimed amounts of nutrients, including phosphate.

Cole differs from the claims in that Cole does not explicitly disclose processes wherein the phosphorus concentration is about 0.008%, as recited in claim 41. However, Cole discloses the desirability of phosphate in the fermentation media used therein. Moreover, nutrient concentrations in fermentation media are result-effective parameters whose values

Art Unit: 1651

are determined through routine experimentation by artisans of ordinary skill. Therefore, the determination of suitable phosphate concentrations, such as recited in claim 41, must be considered *prima facie* obvious absent some demonstration of an unexpected result coming from the use of that concentration. The range of carbon source concentrations recited in claim 50 as amended must also be considered obvious for similar reasons, particularly in view of Cole's explicit disclosure of carbon source concentrations encompassing values up to 5% (see column 10, lines 39-42), the difference between the newly claimed value of "greater than 5%" and 5% being infinitesimal. Thus, the artisan of ordinary skill clearly would have reasonably expected a carbon source concentration of 5.00001%, a value encompassed by the amended claims, to have been useful in Cole's process, in view of Cole's disclosure of the suitability of carbon source concentrations of 5%.

Also, the use of sodium dihydrogen phosphate as the phosphorus source, recited in claim 46, must be considered obvious over Cole's disclosed use of potassium dihydrogen phosphate as the phosphorus source, the artisan of ordinary skill reasonably expecting the salts of potassium and sodium to function substantially equivalently in the processes disclosed by Cole, especially in view of Cole's disclosure that either of

Art Unit: 1651

the salts of phosphoric acid may be used. See column 10, lines 56-57. Lastly, the use of large volume fermentations in the processes disclosed by Cole, recited in claims 53 and 54, must be considered obvious, in view of the fact that it would have been economically desirable to have produced larger quantities of the desired compound. Lastly, allowing the phosphorus concentration to decrease to zero as recited in claim 95 must be considered obvious in view of the fact that the artisan of ordinary skill would have considered it obvious to use only that amount of phosphorus to obtain maximal product yield. A holding of obviousness over the cited claims is required.

All of applicant's argument regarding this ground of rejection has been fully considered but is not persuasive of error. While applicant asserts that no motivation exists for using 0.008% phosphorus in the medium, note specifically that that concentration is within the concentrations disclosed by Cole as being suitable for production of clavulanic acid. As to the allegations of unexpected results, it is respectfully pointed out that, other than the yields described by applicant, the claims under examination are essentially identical or substantially similar to the processes disclosed by Cole. Thus, the alleged unexpected result must be due to some unclaimed aspect of the process disclosed by applicant. In this respect

Art Unit: 1651

note that the processes in applicant's specification contain numerous process parameters and use specific strains, none of which are recited in the claims under examination. Moreover, as to the alleged "addition" of phosphorus, no such step is recited in the claims under examination. Therefore, the allegation of unexpected result is simply not commensurate in scope with the claims under examination.

As to the alleged lack of equivalency between sodium and potassium phosphate salts, note that both salts are notoriously well known to be used in the fermentation arts, and are clearly equivalent, at least to the extent they are both suitable in the preparation of aqueous solutions. Also, with respect to claim 50 and the new limitation regarding carbon source concentration, the artisan of ordinary skill clearly would have reasonably expected a carbon source concentration of 5.00001%, a value encompassed by the amended claims, to have been useful in Cole's process, in view of Cole's disclosure of the suitability of carbon source concentrations of 5%. Lastly, as to the alleged undesirability of using large volume fermentations in Cole's processes, note specifically that although the fermentation takes longer in larger vessels, the fermentation also produces more clavulanic acid. Thus, it is not clear, as asserted by applicant, that the larger fermentation volumes are undesirable.

Art Unit: 1651

If anything, Table I at column 19 demonstrates that it only takes twice as much time to make four times as much product if one uses a larger volume fermenter. In sum, because the cited prior art suggests the claimed process, the holding of obviousness is properly maintained

Claims 36, 38, 41-55 and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cole et al (U.S. Pat. 4,110,165) in view of Stanbury et al (*Principles of Fermentation Technology*, Pergamon Press, New York, 1984, pages 11-25).

As discussed above, Cole is considered to anticipate certain claims, and to render obvious others. Cole does not explicitly disclose conducting the fermentations as fed-batch or continuous processes, as recited in claims 48 and 55. However, Cole clearly discloses that 0.1% is a suitable concentration of phosphorus for fermentative production of clavulanic acid. See Example 13. Thus, the artisan of ordinary skill at the time of applicant's invention clearly would have been motivated by Cole's disclosure of the suitability of 0.1% phosphorus to have ensured the presence of that amount of phosphorus, in continuous or fed-batch processes of the type disclosed by Stanbury. Additional motivation for using the fed-batch systems disclosed by Stanbury would have been derived from the fact that

clavulanic acid is a very similar molecule to penicillin, and Stanbury discloses that fed-batch processes are particularly desirable in fermentations which produce antibiotics such as penicillin. See Stanbury at 23, discussing the applicability of fed-batch fermentation to penicillin production. A holding of obviousness over the cited claims is therefore required.

All of applicant's argument regarding this ground of rejection has been fully considered, but is not persuasive of error. As to the alleged undesirability of using a continuous process for Cole's fermentations, note specifically that although Cole does not exemplify a combination of a continuous process with the claimed phosphorus concentrations, Cole states unequivocally that "[t]he fermentation may also be carried out in a continuous fashion." Column 11, lines 24 and 25.

Moreover, as discussed above with respect to the larger volume fermentations, note specifically that although the fermentation takes longer in larger vessels, the fermentation also produces more clavulanic acid. Thus, it is not clear, as asserted by applicant, that the larger fermentation volumes are undesirable. If anything, Table I at column 19 demonstrates that it only takes twice as much time to make four times as much product if one uses a larger volume fermenter. Lastly, as to the inapplicability to Cole's disclosure of the advantages of fed-

Art Unit: 1651

batch processes in pencillin as disclosed by Stanbury, Stanbury clearly suggests those advantages to be applicable generally to antibiotic production. Cole clearly discloses clavulanic acid to be antibacterial. The rejection must therefore be maintained.

Claims 36, 38, 41-55 and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cole et al (U.S. Pat. 4,110,165) in view of Stanbury et al (*Principles of Fermentation Technology*, Pergamon Press, New York, 1984, pages 11-25), as applied above to claims 36-38 and 41-55, and in further view of Puentes et al (EP 0 182 522 A1).

As discussed above, Cole obviates claims 36-38 and 41-55 when taken in view of Stanbury. With the exception of *Streptomyces clavuligerus*, neither of those references discloses the production of clavulanic acid from all of the microorganisms recited in claim 47. However, Puentes et al disclose that all of the claimed microorganisms were known at the time of applicant's invention to produce clavulanic acid in known media containing carbon sources, nitrogen sources and inorganic salts. See page 2. Thus, the substitution of any known clavulanic acid-producing species for that disclosed in Cole clearly would have been considered an obvious matter of selecting from known

Art Unit: 1651

equivalents, the artisan of ordinary skill reasonably expecting from Puentes that the microorganisms disclosed therein would be able to produce clavulanic acid in the fermentation media disclosed by Cole. Thus, absent some unexpected result inhering from the use of the claimed microorganisms, the claims must be considered obvious in this respect.

All of applicant's argument regarding this ground of rejection has been fully considered but is not persuasive of error. Applicant essentially reiterates the arguments addressed above. These arguments are not found persuasive for the reasons stated above. As to Cole's failure to add phosphorus during the fermentation processes, note that applicant's claims do not contain such as step. As to the differences between Puentes and the claims under examination, applicant's argument does not address the rejection as set forth. Puentes is not cited for the processes disclosed therein, per se. Rather, Puentes is cited for the fact that the claimed strains of microorganisms were known to be clavulanic acid producers, and that therefore, the artisan of ordinary skill would have recognized Puentes' microorganisms to have been suitable in Cole's clavulanic acid production processes. Contrary to applicant's argument, such an analysis is evident from the cited prior art, and does not require any hindsight reasoning. Moreover, to the extent that

Art Unit: 1651

applicant fails to address the combination of references as put forth in the rejection, it is respectfully pointed out that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

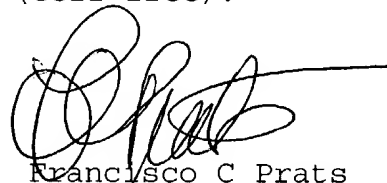
Art Unit: 1651

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Francisco C Prats whose telephone number is 571-272-0921. The examiner can normally be reached on Monday through Friday, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read 'F. Prats', with a long horizontal line extending to the right.

Francisco C Prats
Primary Examiner
Art Unit 1651

FCP